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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
ANDERSON, JAMES D

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
07/13/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

nyuspatactions@ladas.com

Office Action Summary	Application No.	Applicant(s)	
	10/651,307	WANG ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *115,122,124-129 and 136-147* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *115, 122, 124-129, and 136-147* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 10/8/2009, are acknowledged and entered. Claims 115, 122, 124-129, and 136-147 are pending and under examination.

Change of Examiner

The examiner assigned to the instant application has changed. The new examiner is James D. Anderson. Contact information is provided at the end of this Office Action.

Response to Arguments

Applicants' arguments, filed 10/8/2009, have been fully considered and are persuasive to overcome the rejections of record. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112 – 2nd Paragraph – New Ground of Rejection

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 115, 122, and 136-147 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

"The primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent. A secondary purpose is to provide a clear measure of what applicants regard as the invention so that it can be determined whether the claimed invention meets all the criteria for patentability and whether the specification meets the criteria of 35 U.S.C. 112, first paragraph with respect to the claimed invention.", (see MPEP § 2173).

In the instant case, the recited "...said dose being at least 10^6 Gy within a distance of up to 10 Angstroms from the iodine in the rose bengal...." is unclear with respect to whether the "said dose" refers to the dose of x-rays or the dose of Auger electrons released from rose bengal upon contact with x-rays.

Claims 124-129 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

"The primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent. A secondary purpose is to provide a clear measure of what applicants regard as the invention so that it can be determined whether the claimed invention meets all the criteria for patentability and whether the specification meets the criteria of 35 U.S.C. 112, first paragraph with respect to the claimed invention.", (see MPEP § 2173).

In the instant case, claims 124-129 depend from cancelled claim 123. As such, the metes and bounds of the claims are not clearly defined.

Claim Rejections - 35 USC § 103 – New Ground of Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 115, 122, and 136-147 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Dees *et al.*** (WO 00/37927; Published June 29, 2000) (newly cited) and **Cash *et al.*** (USP No. 6,366,801 B1; Issued Apr. 2, 2002; Filed Apr. 14, 2000) in view of **Laster *et al.*** (Reference AS in IDS filed 10/27/2003).

Claimed Invention

The instant claims recite methods of preferential destruction of tumor cells in a subject comprising administering rose bengal to the subject such that the rose bengal accumulates in lysosomes of cells of the subject and then irradiating a specific location of the subject comprising a tumor with an x-ray tube that emits monochromatic line emission x-rays having an energy above and near the K-absorption edge or L-absorption edge of iodine that is present in the rose bengal so as to cause emission of Auger electrons from the rose bengal accumulated in the lysosomes of irradiated cells in the specific location, said dose being at least 106 Gy within a distance of up to 10 Angstroms from the iodine in the rose bengal, said irradiating being confined to the specific location comprising the tumor so as to localize damage caused by the irradiating and to minimize damage to normal cells of the subject (Claim 1).

Teachings of Dees et al.

Dees *et al.* disclose high energy phototherapeutic agents or radiosensitizer agents comprised of a halogenated xanthene and methods of treating and imaging using radiosensitizer agents in diseased tissue, particularly cancerous tumors (Abstract; page 1, lines 4-7).

The therapeutic performance of a radiosensitizer is disclosed to primarily be a function of enhanced absorption of the applied radiation dose in sensitized tissues relative to that in non-sensitized tissues. This differential absorption is commonly effected by the use of agents having a high absorption cross-section for a particular type of radiation (such as x-rays). For example, Dees *et al.* disclose that metal or halogen atoms are often used, either in atomic form or incorporated into a molecular carrier, due to their secondary radiative emissions, ionization, and

other chemical or physical processes that increase the localized cytotoxicity of the applied energy (i.e., radiation-induced cell death, or "light cytotoxicity") (page 2, lines 22-30).

In some embodiments of the invention, the halogenated xanthene radiosensitizer agent also acts as an imaging contrast agent (page 4, lines 10-11). Dees *et al.* disclose the steps of administering a radiosensitizing agent, preferably a halogenated xanthene, a portion of radiosensitizing agent being retained in diseased tissue and treating the diseased tissue with x-rays or other ionizing radiation to activate the radiosensitizer agent in the diseased tissue (page 4, lines 18-22).

Dees *et al.* teach that radio dense agents, such as halogenated xanthenes, which exhibit a preference for concentration in cellular membranes and other key components and structures of diseased tissue, will exhibit additional therapeutic dose enhancement over that possible with previously known agents as a result of increased radiosensitization yield of such agents owing to improved proximity of such agents, upon interaction with diseased tissue, to sensitive structures during irradiation and subsequent radiosensitization (page 5, lines 6-13).

Regarding the claimed rose bengal, Dees *et al.* disclose that rose bengal is a preferred halogenated xanthene radiosensitizing agent for use in the methods disclosed therein and that rose bengal partitions into cell walls (page 4, lines 7-9; Figure 1a; page 5, line 30 to page 6, line 8). Dees *et al.* disclose that rose bengal has been found to accumulate preferentially in some tumors and other diseased tissues (page 6, lines 28-30) and that rose bengal can be dissolved in aqueous solution at high concentrations while retaining a significant preference for hydrophobic environments, such as within cell membranes (page 6, line 33 to page 7, line 3).

Regarding the claimed administration of rose bengal to the subject, Dees *et al.* disclose targeting of the radiosensitizing agents is effected by chemical partitioning of the agent at, near, or into the target by controlled agent delivery at, near, or into the target such as by localized delivery via injection, flooding, or spraying (page 5, line 30 to page 6, line 8). Dees *et al.* further disclose that in a preferred embodiment of the invention, at least one halogenated xanthene is used as an x-ray sensitizer or radiosensitizer agent for treatment of diseased tissue using radiosensitization by administering the agent orally, systemically, or topically prior to radiosensitization (page 8, lines 4-12).

Regarding the claimed irradiating a specific location of the subject comprising a tumor with an x-ray tube that emits monochromatic line emission x–rays having an energy above and near the K-absorption of iodine that is present in the rose bengal, Dees *et al.* disclose that strong absorption for the halogens of the halogenated xanthenes occurs well below the energies used for standard diagnostic or therapeutic x-ray devices, which generally use energies greater than 30 kEv (page 7, lines 22-26, Figure 4). Accordingly, Dees et al. disclose that it is preferred that x-rays or other ionizing radiation with energy equal to or greater than approximately 1 keV and less than or equal to 1000 MeV be used to activate the agent. Preferably, the agent is activated using x-rays having an energy in excess of 30 keV (page 8, lines 10-12).

Teachings of Cash et al.

Cash *et al.* disclose that contrast agents developed specifically for x-ray diagnostics provide dose-enhanced radiotherapy and radiosurgery due to the presence of heavy metal elements from these contrast agents leading to major dose increase in target tissue (Abstract). Cash *et al.* thus disclose increased enhancement in the local x-ray dose to a target tumor can be created with the correct combination of x-rays and contrast agents. Constrast agents, which comprise a heavy metal element, *e.g.*, iodine, are introduced into the patient either by direct injection or intravenously (col. 2, lines 62-67).

Typical contrast agents for use in the invention comprise a compound that contains a large percentage of a heavy metal element, *e.g.*, iodine (col. 3, lines 1-5).

Cash *et al.* disclose a method comprising: i) visualizing a tumor; ii) delivering a contrast agent into the tumor or into a surface portion of the tumor; iii) calibrating the amount of contrast agent in the tumor; and iv) irradiating the tumor by a low-energy, orthovoltage x-ray source before the contrast agent leaks from the tumor (col. 3, lines 11-27). Cash *et al.* disclose that an x-ray beam having an energy level of from about 40 keV to about 80 keV is used and focused by a mirror array (col. 4, lines 51-54).

Cash et al. disclose that when an x-ray encounters an atom it interacts through one of three mechanisms: photoelectric absorption, elastic scattering, or Compton scattering. (col. 5, lines 47-49). Photoelectric absorption is disclosed to dominate at low energy (col. 5, lines 51-52) and is the most efficient for conversion of x-ray energy to ionization in the body (col. 6, lines 5-

6). In this regard, Cash et al. disclose that the energy of the photon in excess of the K-edge energy is deposited in the primary photoelectron and thus causes ionization in the body and the K-edge energy remaining in the atom is released through the emission of either a fluorescent x-ray or an Auger electron. If released as an Auger electron, then all the K-edge energy is contained in this second electron and causes tissue damage (col. 6, lines 6-13).

Regarding contrast agents, Cash et al. disclose that the desired effect can only be achieved by having heavy elements present in large amounts at the tumor site. In this regard, Cash et al. teach that to obtain a major increase in photoelectric absorption from an element at x-ray energies that penetrate significant distances into the body, the absorbing element should have an atomic number of 50 or more, e.g., iodine (col. 6, lines 48-56). Regarding iodine, Cash et al. disclose that iodine is a common element in contrast media with a K-edge at 33.2 keV. At this low energy, x-rays penetrate only a short distance into the body so x-rays sources are mostly configured to operate at energies above 34 keV (col. 6, lines 63-67).

Regarding administering directly to a specific organ or tissue of a subject containing tumor cells, Cash et al. disclose high levels of dose enhancement are achieved when contrast agent is injected directly into the tumor or into a portion of its surface (col. 7, lines 57-62; col. 8, lines 14-39).

Teachings of Laster et al.

While Dees *et al.* and Cash *et al.* do not explicitly disclose the use of an x-ray that emits monochromatic line emission x-rays as recited in the instant claims, Laster *et al.* teaches that activation of halogens in halogenated pyrimidines by monochromatic photons above the K absorption edge of the halogens was known in the art prior to Applicant's invention. In fact, the combined effect of Auger electrons and monochromatic photons has been studied extensively in the prior art (page 219, left and right columns).

> In 1977, Tisljar-Lentulis and coworkers postulated the use of stable halogenated pyrimidines incorporated in cellular DNA as potential agents for inducing an Auger effect. **Activation of the halogen by monochromatic photons above its K absorption edge would result in photoelectric absorption leading to the release of Auger electrons**. These low-energy electrons would contribute additional ionization within the DNA.

> .....several investigators have attempted to demonstrate the increased biological effectiveness which would result from the combined effect, of the Auger electrons and monochromatic photons.
>
> Fairchild et al. described photon activation therapy as a potential clinical modality for the treatment of malignant brain tumors (20). Photon activation therapy is a binary therapy that uses stable IdUrd for two purposes: (a) as radiosensitizer and (b) as a molecular carrier of iodine into the DNA. **The latter becomes the source of Auger electrons when activated by photons with an appropriate energy**.

Laster *et al.* teaches administration of an iodine-containing agent to Chinese hamster V79 cells and subsequent irradiation of the cells with monochromatic x-rays having an energy above the K-edge of iodine (pages 220-223).

Examiner's Determination of Obviousness

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of Applicant's invention to have used rose bengal as a radiosensitizing/contrast agent in the treatment tumors as suggested and motivated by the teachings of the cited prior art.

In making the determination that the claimed invention would have been obvious to one of ordinary skill in the art at the time the invention was made, the Examiner makes the following findings of fact:

I. Halogenated xanthenes, preferably rose bengal, are taught by Dees *et al.* to be useful as radiosensitizing/contrast agents useful in the treatment of tumors when irradiated with x-rays (page 4, lines 7-9; Figure 1a; page 5, line 30 to page 6, line 8);

II. Rose bengal was known to accumulate in tumors and other diseased tissue (Dees *et al.* at page 6, lines 28-30);

III. Administration of x-rays at or above the K-edge absorption of the halogen contained in halogenated agents leads to ionization in the body and the K-edge energy remaining in the atom is released through the emission of either a fluorescent x-ray or an Auger electron. If released as an Auger electron, then all the K-edge energy is contained in this second electron and causes tissue damage (Cash *et al.* at col. 6, lines 6-13);

IV. Combined use of monochromatic photons from x-rays and halogenated pyrimidines to cause photoelectric absorption and release of Auger electrons was known in the art prior to Applicant's invention (Laster *et al.* at page 219).

In view of the teachings of the cited prior art and the above findings of fact, the Examiner has determined that Applicant's claimed method of i) administering rose bengal to a subject such that the rose bengal accumulates in lysosomes of cells of the subject; and 2) irradiating a specific location of the subject comprising a tumor with x-ray that emits monochromatic line emission x-rays having an energy above and near the K-absorption edge of iodine that is present in rose bengal would have been *prima facie* obvious to one skilled in the art at the time of Applicant's invention.

The skilled artisan would predict that irradiation of rose bengal present in tumor cells of a subject would result in photoelectric absorption and release of Auger electrons that would preferentially destroy tumor cells as recited in the instant claims based upon the teachings of Dees *et al.* and Cash *et al.* in view of the teachings of Laster *et al.*

Regarding Applicant's Jepson claims (claims 141-147), Applicant's claimed improvement upon known methods of treating tumors with x-ray radiation and a radiosensitizing agent would have been *prima facie* obvious because the claimed rose bengal is disclosed in the prior art as a suitable radiosensitizing agent and monochromatic x-rays administered at an energy above and near the K-absorption edge of iodine present in rose bengal is taught in the cited prior art.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. USP No. 6,331,286 to Dees *et al.* discloses and claims methods of treating tumors and cancer comprising administering rose bengal to or into a tumor or cancer diseased tissue and treating the tumor or diseased cancer tissue with ionizing radiation having an energy between 1 kiloelectron volt and 1000 megaelectron volts so as to activate the rose bengal in the tumor or cancer diseased tissue (see claims 1-33 of USP No. 6,331,286). The disclosure of USP No.

6,331,286 to Dees *et al*. is identical to the disclosure of WO 00/37927 to Dees *et al*. used in the above 35 U.S.C. 103 rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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